NIEHS
National Institute of Environmental Health Sciences

Keynote for the 12th Annual Research and Education and Public Policy Forum

February 19 2006

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U.S. Department of Health and Human Services
National Institute of Health
National Institute of Environmental Health Services

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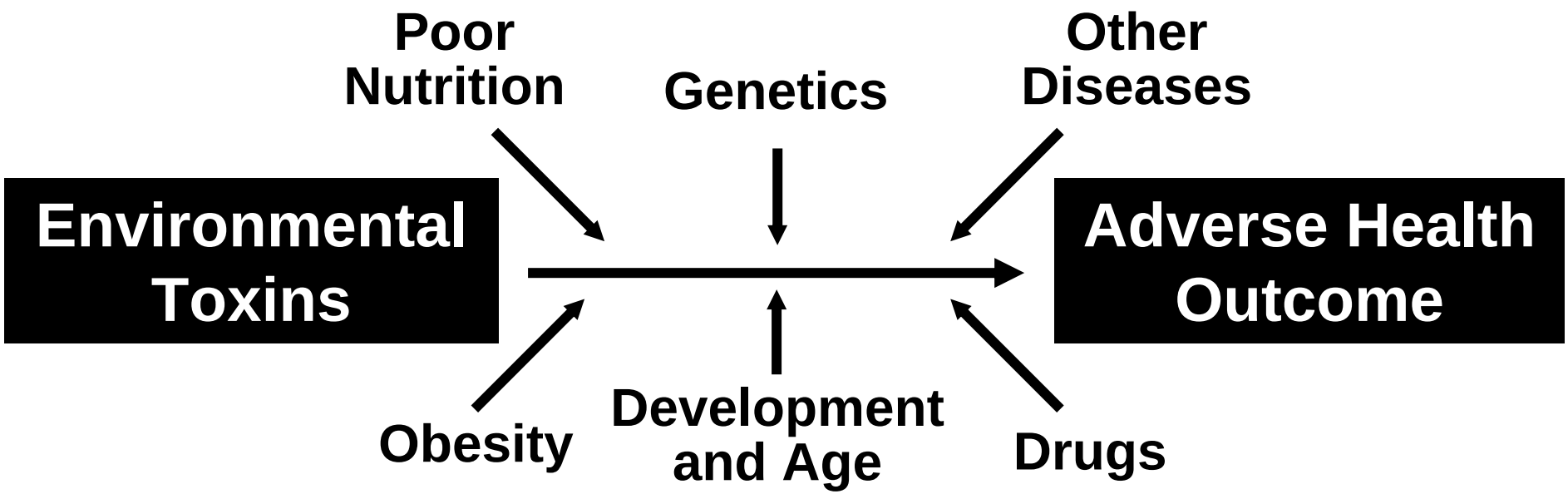
- Environmental Exposures and Parkinson's Disease
- Role of NIEHS in Parkinson's Research Program
- Priorities for Program Development

U.S. Department of Health and Human Services
National Institute of Health
National Institute of Environmental Health Services

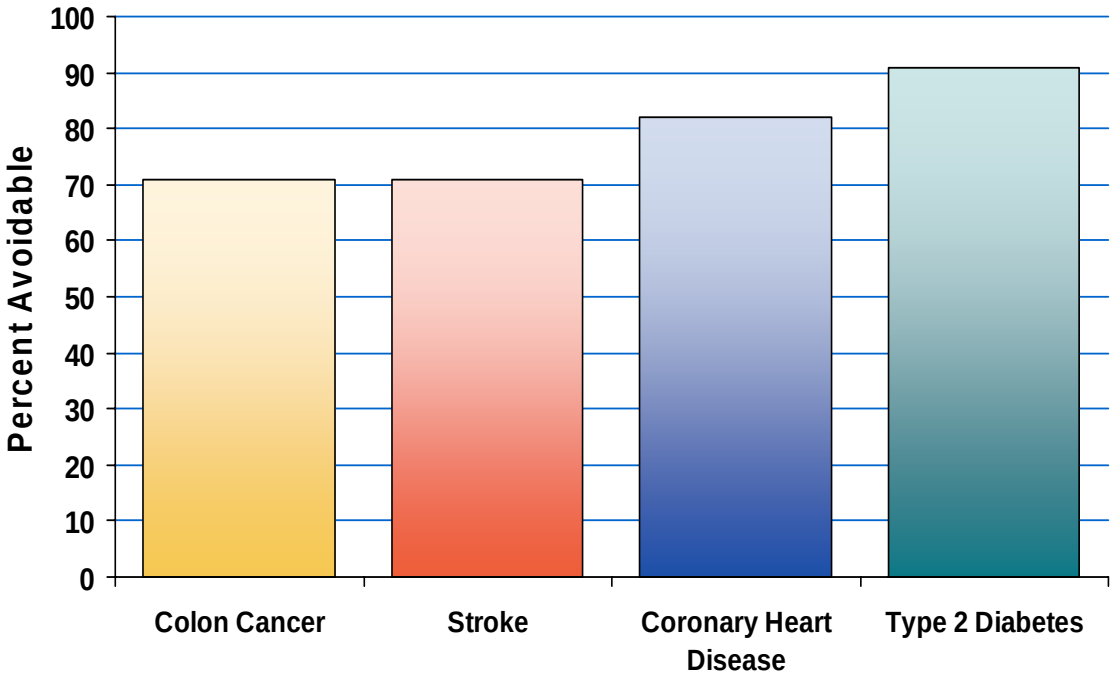
Vision for NIEHS

Use environmental sciences to understand human disease and improve human health

Why do some people exposed to an environmental agents develop disease and others do not?



Complex Human Diseases: Challenge and Opportunity



- 70-90% of the major diseases in the USA are caused by reversible behaviors and exposures
- Single gene mutations are the major cause of cancers and CVD in < 5% of the cases

Willett. *Science* 2002; 296:695

Human Diseases Relevant to NIEHS

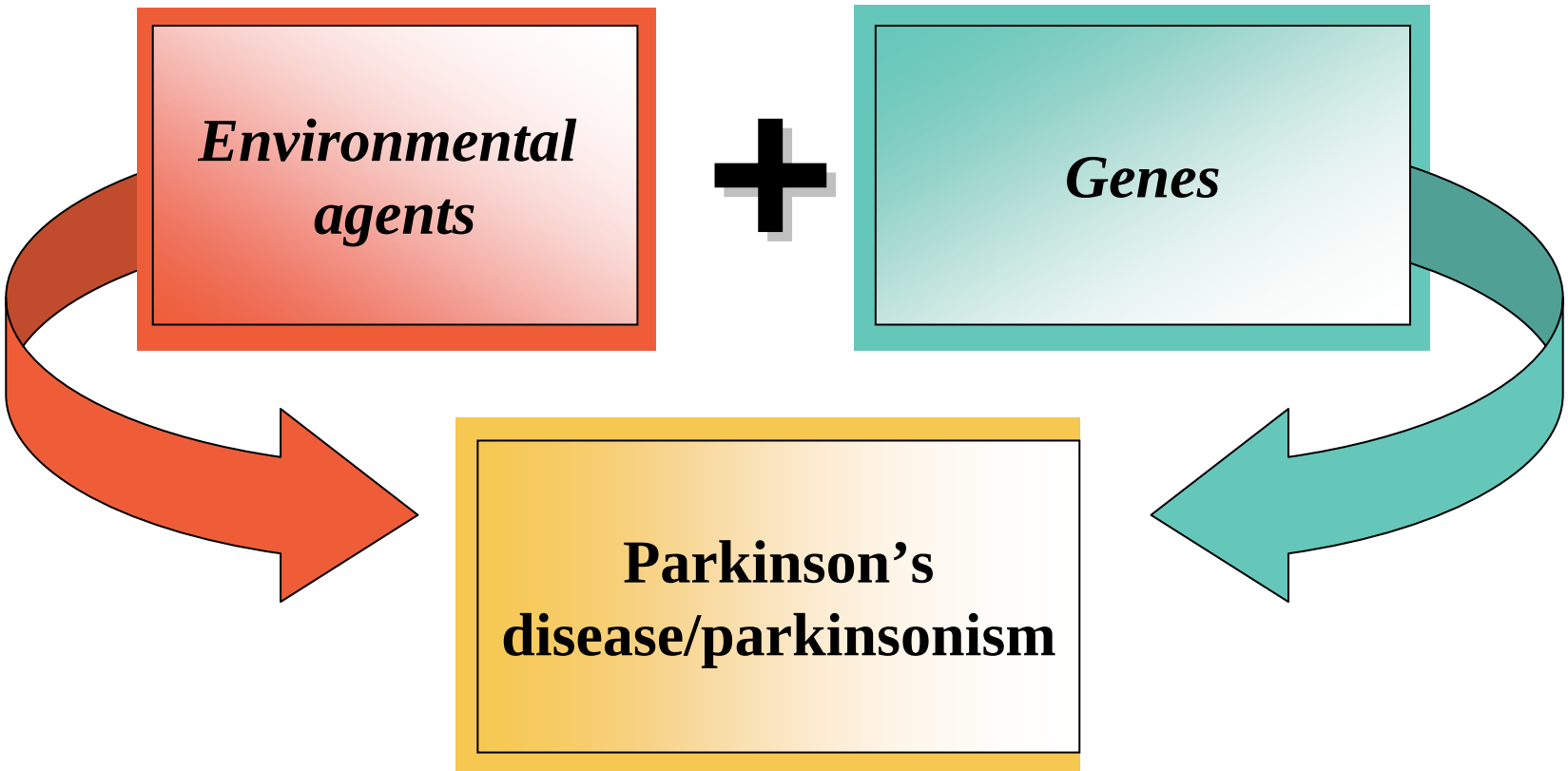
- **Any disease where environmental agents contribute to the cause or pathogenesis of the disease process**
- **NIEHS shares interests with many other NIH institutes**
  - **Parkinson's disease and neurodegenerative disorders**
  - **Asthma and pulmonary disease**
  - **Reproductive and endocrine disorders**
  - **Immune and autoimmune disorders**
  - **Birth defects and developmental disorders**
  - **Cardiovascular disease**
  - **Obesity**
  - **Breast cancer**

Role of NIEHS in Parkinson's Disease

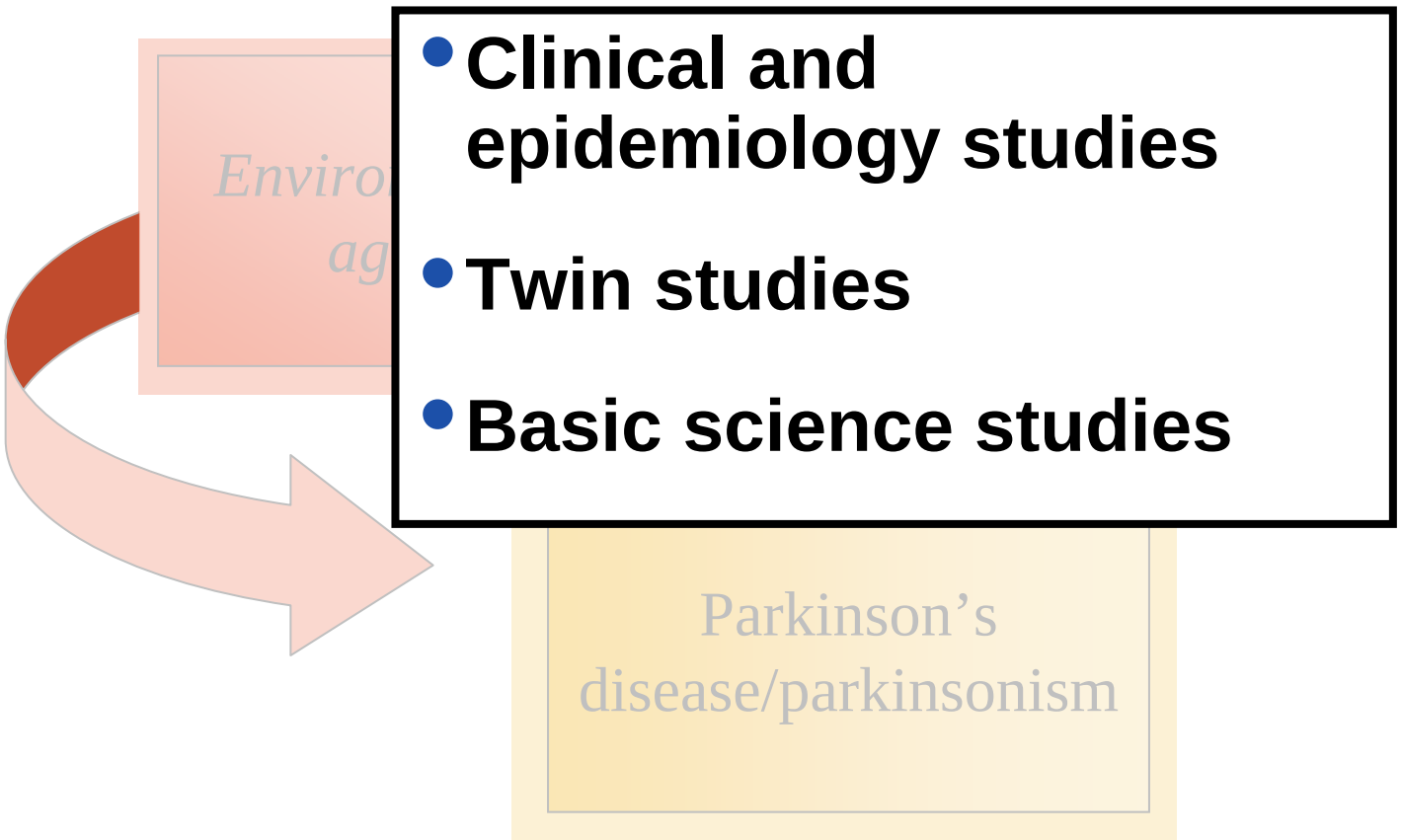
Several new initiatives led to an increase in the number of NIEHS-supported PD grants

- **1999: Xenobiotics and Cell Death/Injury in Neurodegenerative Disease**
- **2000: Role of the Environment in PD**
- **2001: Mitochondrial Function and Neurodegeneration (with NINDS)**
- **2002: Fast track Grants for PD (with NINDS and others)**
- **2002: Collaborative Centers PD Program**
- **2003: Gene-Environment interaction in Neurodegenerative Disease**

Etiology of Parkinson's Disease



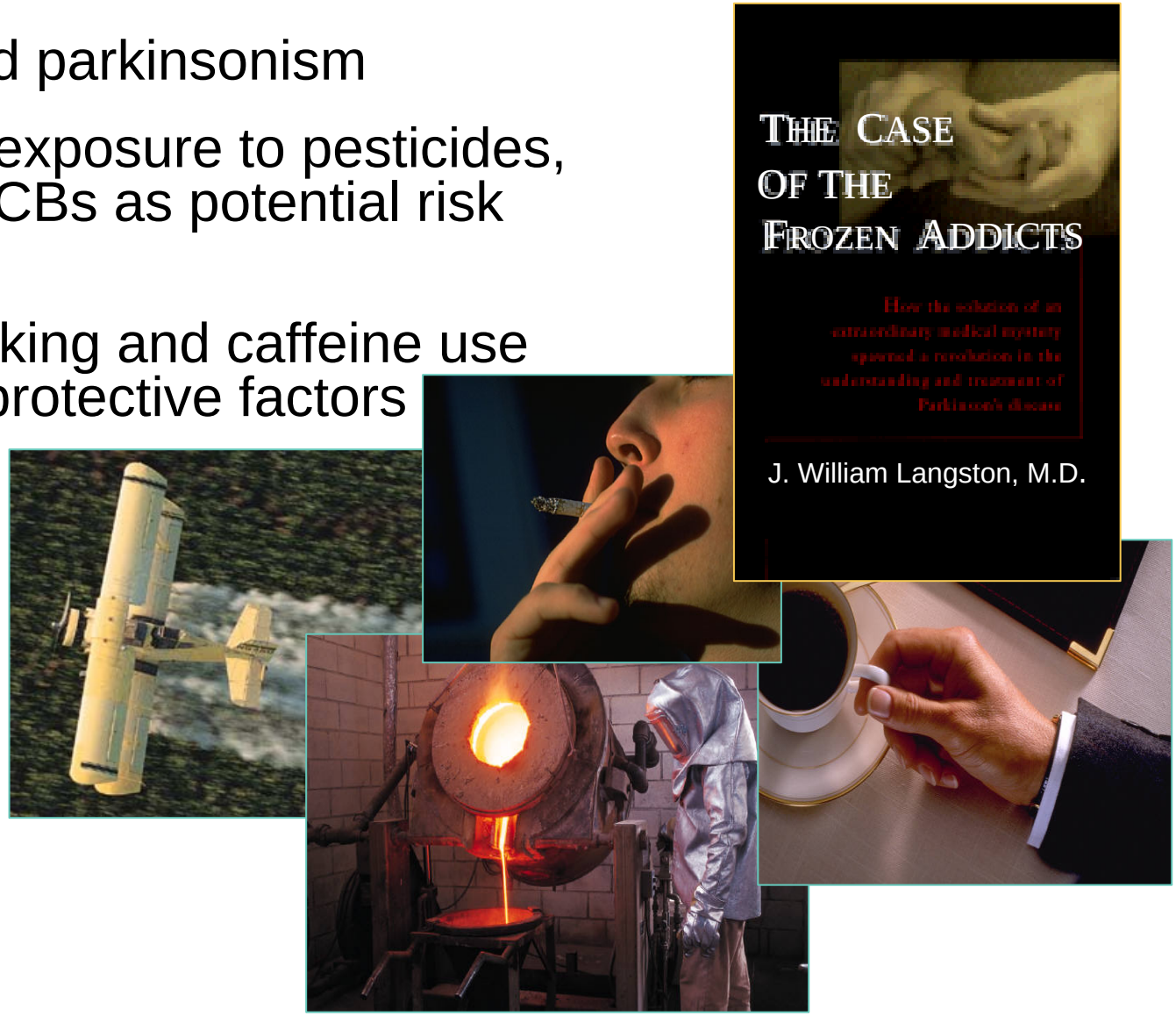
Environmental Contribution to Parkinson's Disease



- **Clinical and epidemiology studies**
- **Twin studies**
- **Basic science studies**

Clinical and Epidemiology Studies

- MPTP-induced parkinsonism
- Occupational exposure to pesticides, metals, and PCBs as potential risk factors
- Cigarette smoking and caffeine use appear to be protective factors



Twin Studies

No evidence for heritability of Parkinson disease in Swedish twins

Karin Wirdefeldt, MD, PhD; Margaret Gatz, PhD; Martin Schalling, MD, PhD; and Nancy L. Pedersen, PhD

Neurology, July 27, 2004 Jul 27 - Vol 63, No. 2.

, they explain only a small
ity of PD in same-sexed and
born in 1950 or earlier and
pairs for PD by telephone
lred forty-seven twins with
and 517 twins who reported
r movement disorder") were
otic. Similarly, concordances
with suspected parkinsonism
f genetic and environmental
g structural equation model
at environmental factors are
e of genetic effects in PD is
tudying environmental risk

ORIGINAL CONTRIBUTION

Parkinson Disease in Twins

An Etiologic Study

JAMA, January 27, 1999 - Vol 281, No. 4

Caroline M. Tanner, MD, PhD
Ruth Ottman, PhD
Samuel M. Goldman, MD, MPH
Jonas Ellenberg, PhD
Piu Chan, MD, PhD
Richard Mayeux, MSc, MD
J. William Langston, MD

Context The cause of Parkinson disease (PD) is unknown. Genetic linkages have been identified in families with PD, but whether most PD is inherited has not been determined.

Objective To assess genetic inheritance of PD by studying monozygotic (MZ) and dizygotic (DZ) twin pairs.

Design Twin study comparing concordance rates of PD in MZ and DZ twin pairs.

Setting and Participants A total of 19 842 white male twins enrolled in the National Academy of Sciences/National Research Council World War II Veteran Twins Registry were screened for PD and standard diagnostic criteria for PD were applied. Zygosity was determined by polymerase chain reaction or questionnaire.

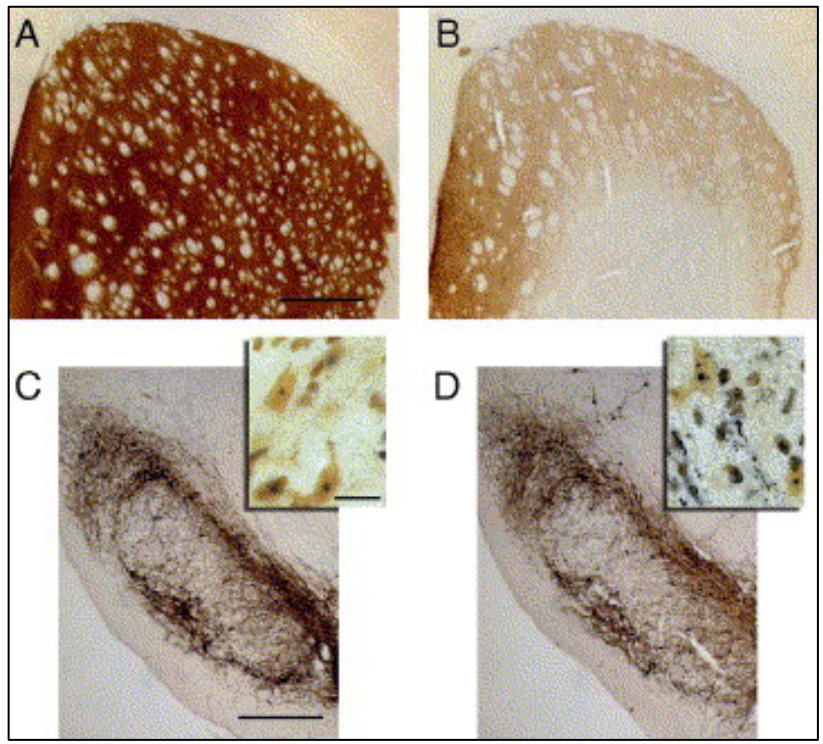
Main Outcome Measure Parkinson disease concordance in twin pairs, stratified by zygosity and age at diagnosis.

Results Of 268 twins with suspected parkinsonism and 250 presumed unaffected twin brothers, 193 twins with PD were identified (concordance-adjusted prevalence, 8.67/1000). In 71 MZ and 90 DZ pairs with complete diagnoses, pairwise concor-

THE IMPORTANCE OF INHERITANCE in the origin of Parkinson disease (PD) has been debated for more than a century. In the early 1980s, interest in an environmental cause of PD was spurred by the identification of biologi-

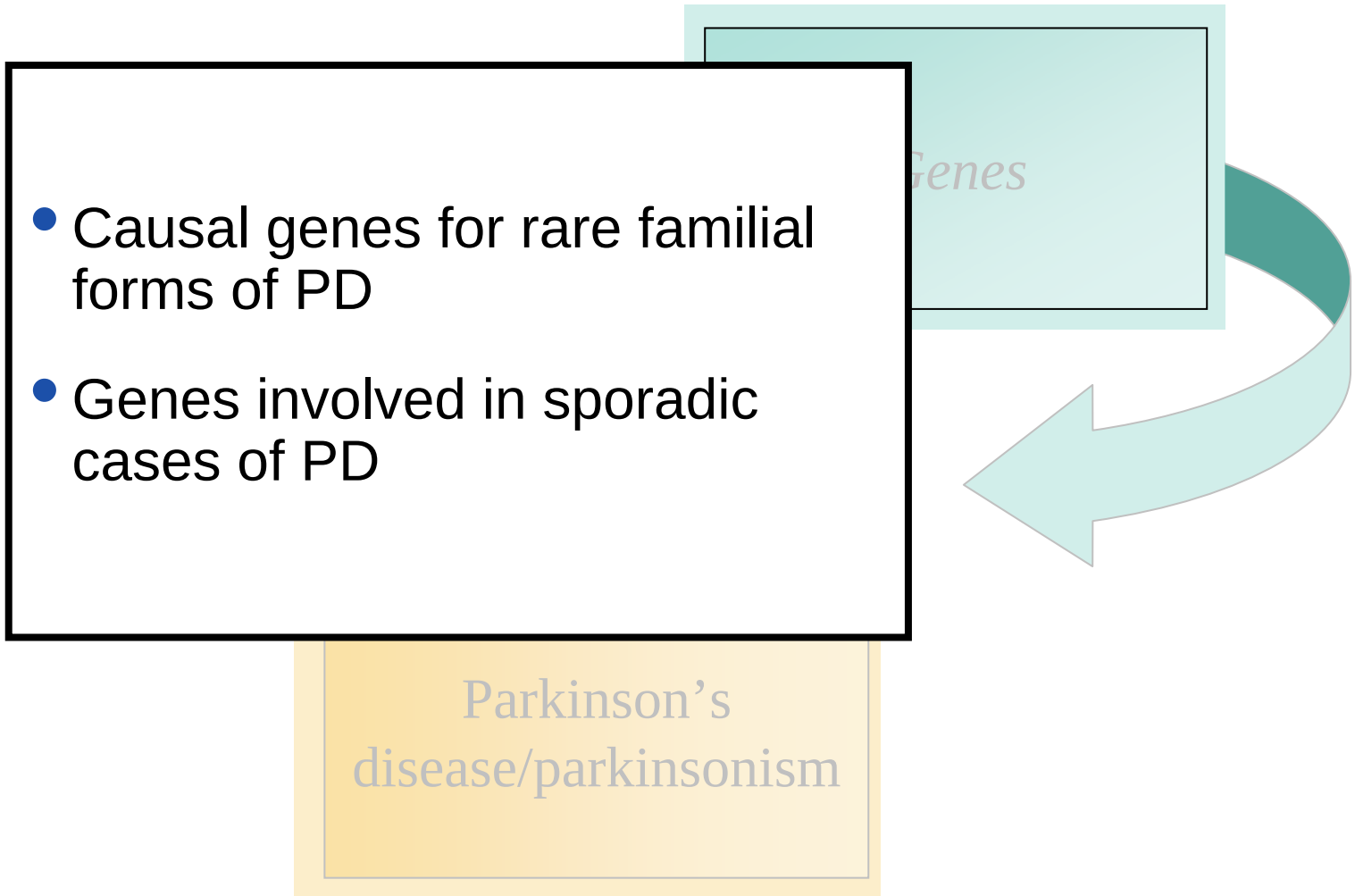
Basic Science Studies

- Creation of toxicant-induced animal models of PD
  - MPTP
  - Rotenone
  - Paraquat/maneb
  - Proteasomal inhibitors
- Toxins recapitulate mechanisms of neurotoxicity observed in PD
  - Mitochondrial dysfunction
  - Oxidant stress



Rotenone-induced nigral degeneration and Lewy-like bodies in DA neurons Betarbet. Neuro Dis, 2006

Genetic Contribution to Parkinson's Disease



- Causal genes for rare familial forms of PD
- Genes involved in sporadic cases of PD

Causal Genes for Rare Familial of PD

Analysis of large nuclear families with many affected individuals have revealed several single gene mutations/locus replications that cause PD

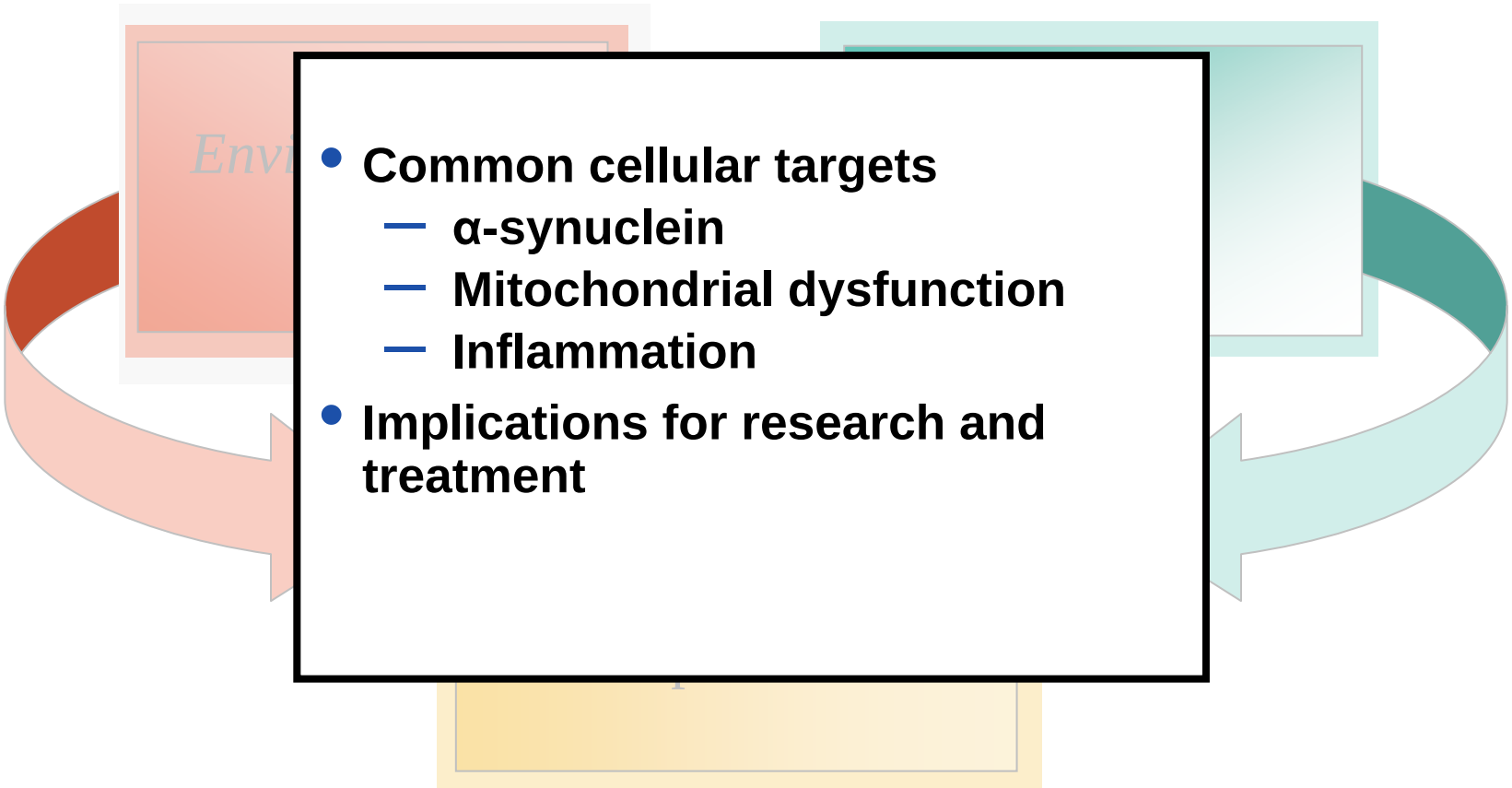
- α-synuclein
- Parkin
- DJ-1
- PINK
- LRRK2
- UCHL1?

Simplified pedigree demonstrating linkage to the parkin Ex3Δ40 mutation. Munhoz. Arch Neurol 2004;61:701.

Genes Associated with Sporadic Late Onset Parkinson's Disease

- **Some positive findings**
  - Tau H1 haplotype
  - α-synuclein promoter variant
  - UCHL1 variant
  - Vesicular monoamine transporter-2 (VMAT2)
  - LRRK2
- **Inconsistent results with many other genes**
- **Slow progress reflects methodologic difficulties, limitations of study designs**

Gene-Environment Interactions



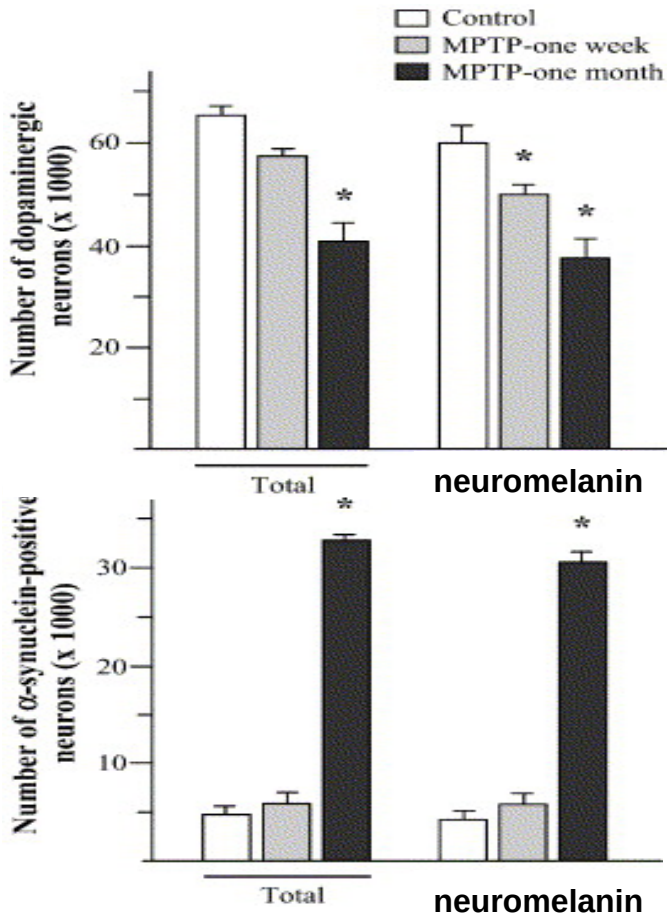
- Common cellular targets
  - α-synuclein
  - Mitochondrial dysfunction
  - Inflammation
- Implications for research and treatment

Benefits from the Identification of Concordant GXE Pathways in PD

- **Focuses on causes and prevention of Parkinson's Disease**
- **Creates integrative research opportunities**
- **Identifies targets for intervention strategies**

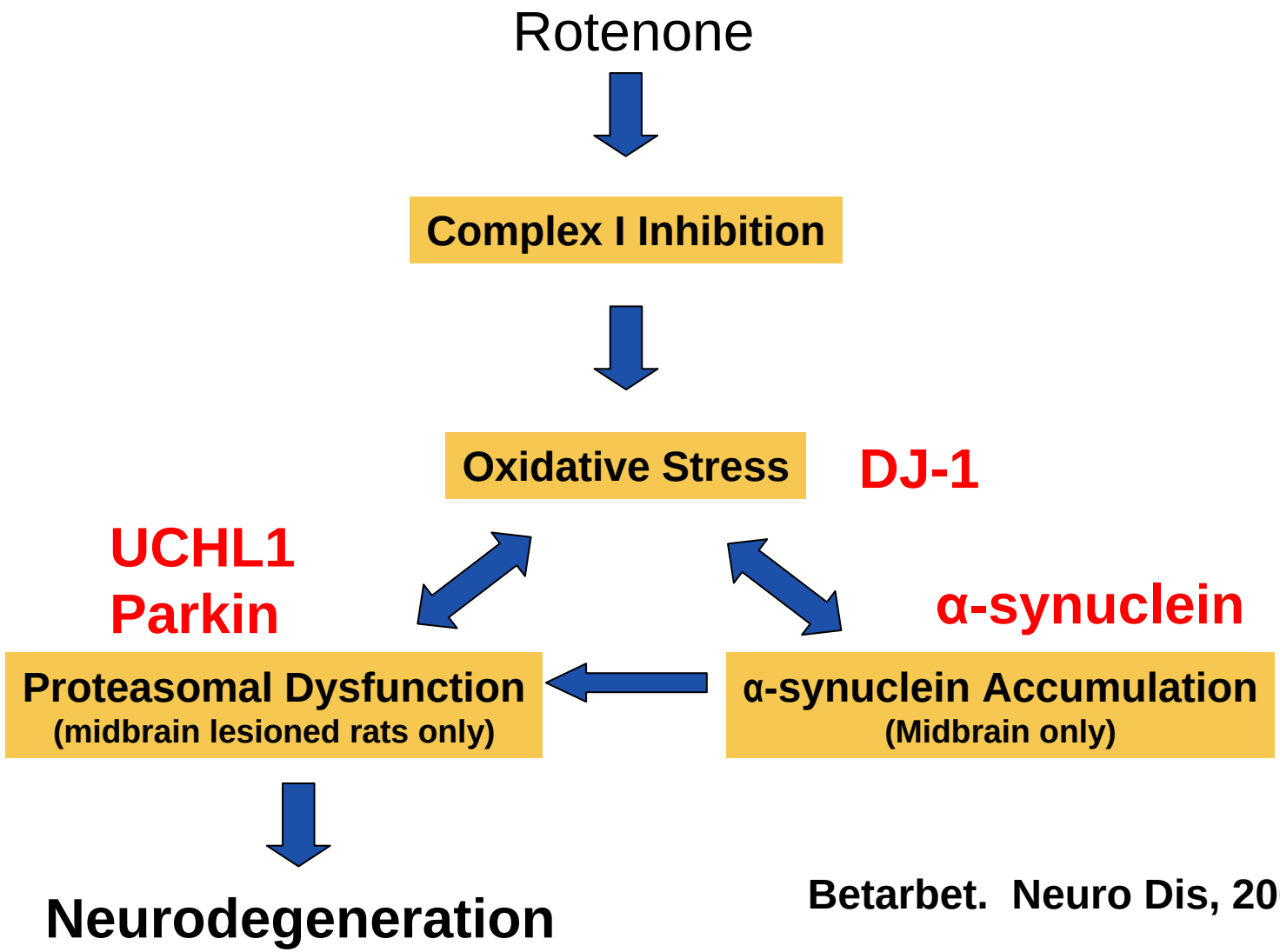
α-synuclein and MPTP Interactions

- Human studies suggest that mutations and overexpression of α-synuclein cause PD
- α-synuclein upregulation occurs in response to toxin exposure and subsequent degeneration
- MPTP recently shown to cause dopaminergic neuronal death and sustained increase in α-synuclein expression in non-human primates



Purisai. Neurobiol Dis 2005; 20:898

Mechanisms of Rotenone Toxicity



Betarbet. Neuro Dis, 2006

Inflammation and Parkinson's Disease

- Postmortem brains in PD often show active inflammation
- Inflammation-associated gene variants (ELAV4) may influence age of onset in PD
- Several toxins (rotenone, MPTP, and LPS) are associated with increases in inflammation and death of dopaminergic neurons
- Anti-inflammatory agents are protective in some animal models
- Consideration in human trials

Morphinian (3H) protects dopaminergic neurons from LPS toxicity
Zhang. Faseb 2005;19:395.

Needs in Gene-Environment Research for PD

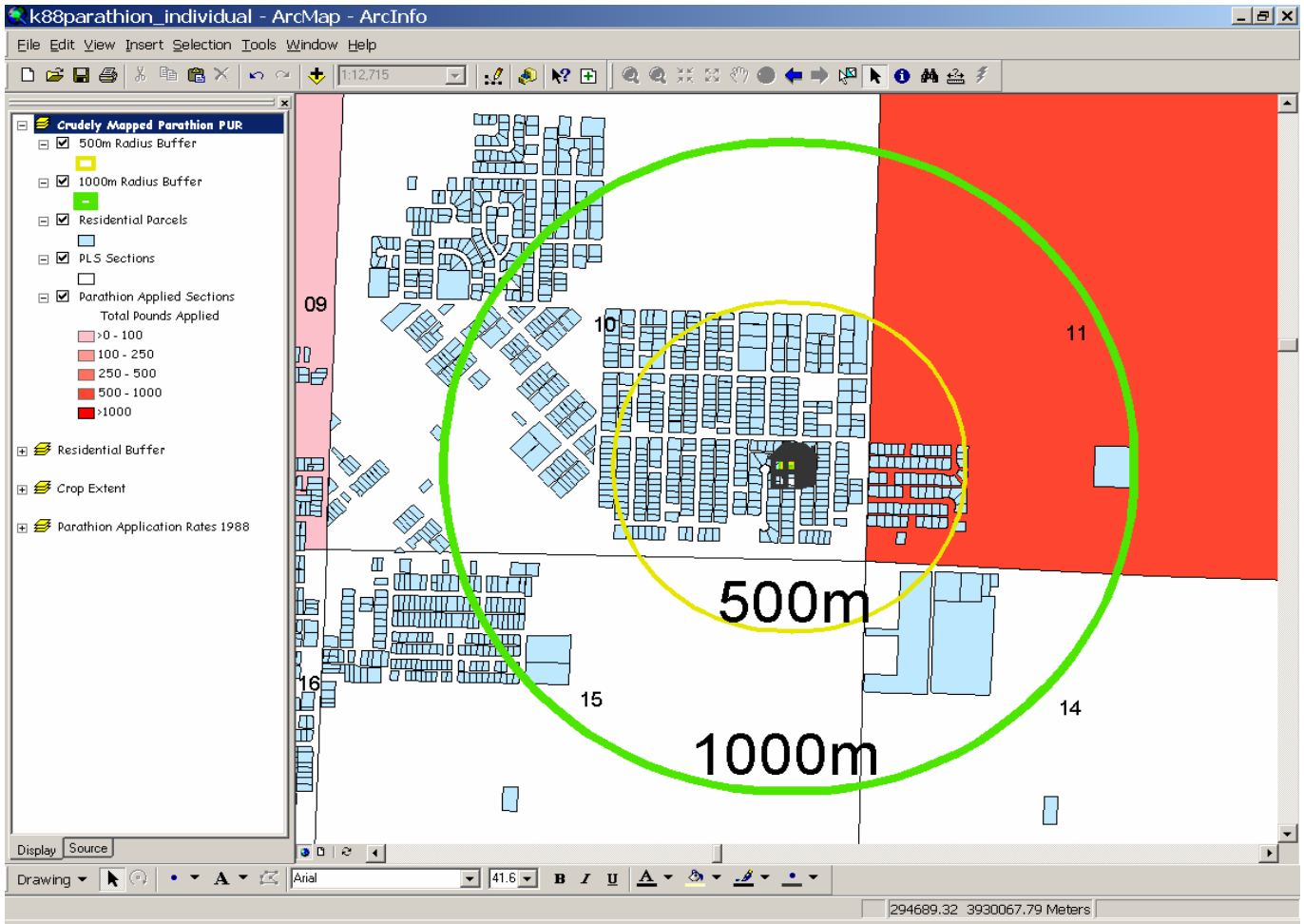
- More precise measures of exposure
- Better animal models of GXE interactions
- Biomarkers of disease
- Uniform methods for PD diagnosis and characterization across studies
- Methods to detect multiple susceptibility genes with small effects

Parkinson's Environment and Gene (PEG) Study

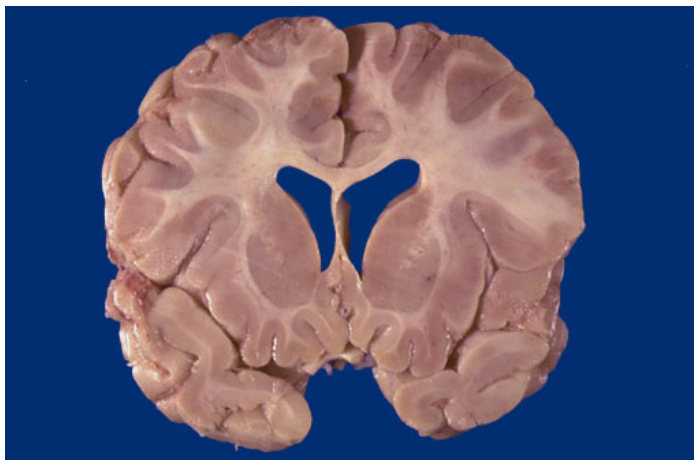
B. Ritz, UCLA

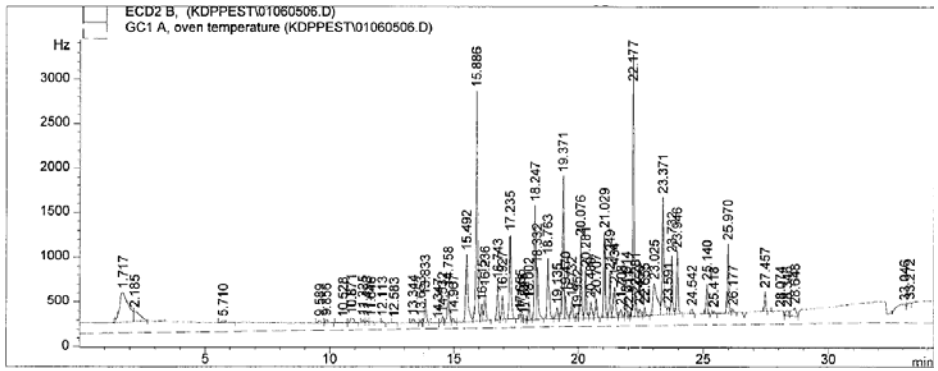
- PEG study
  - Identify all newly diagnosed cases of PD (2001-2005)
  - 400 cases and >400 controls
- Establish a lifetime history of exposure to pesticides
  - recollections of residential history
  - historical exposure records or pesticide use
- Collect biological samples
  - DNA for genotyping

PEG Study: California Pesticide Use Reporting System enables mapping of historical pesticide and crop use



Improved methods for toxin identification in human postmortem brain



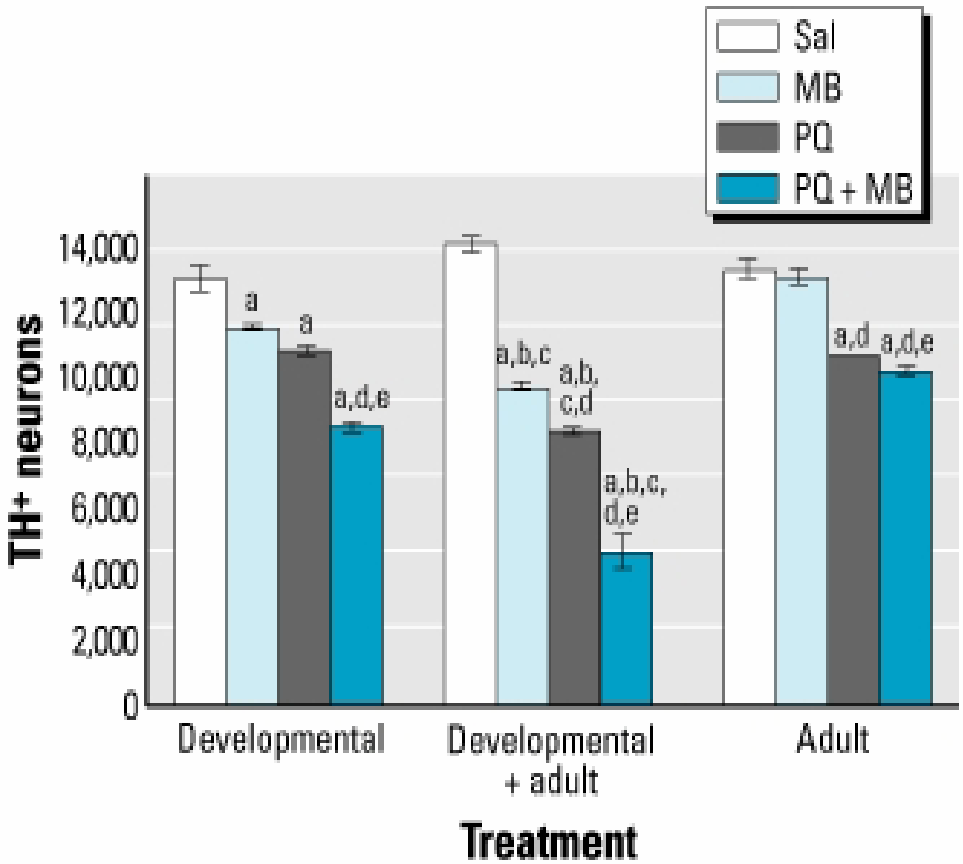


GC/MS analysis of environmental chemicals in neuropathologically-confirmed postmortem PD cases

Ongoing study by Gary Miller, Emory University

Improved Animal Models of PD: long latency and mixed exposure effects

- Gestational exposure to a pesticide mixture (paraquat and maneb) can increase vulnerability of dopamine neurons (TH+) to exposures occurring later in life
- Effects of early exposures to pesticides may be silent until adult re-challenge
- Results suggest that childhood exposures may be informative in epidemiology studies of PD



Debbie Cory-Slechta. RWJ

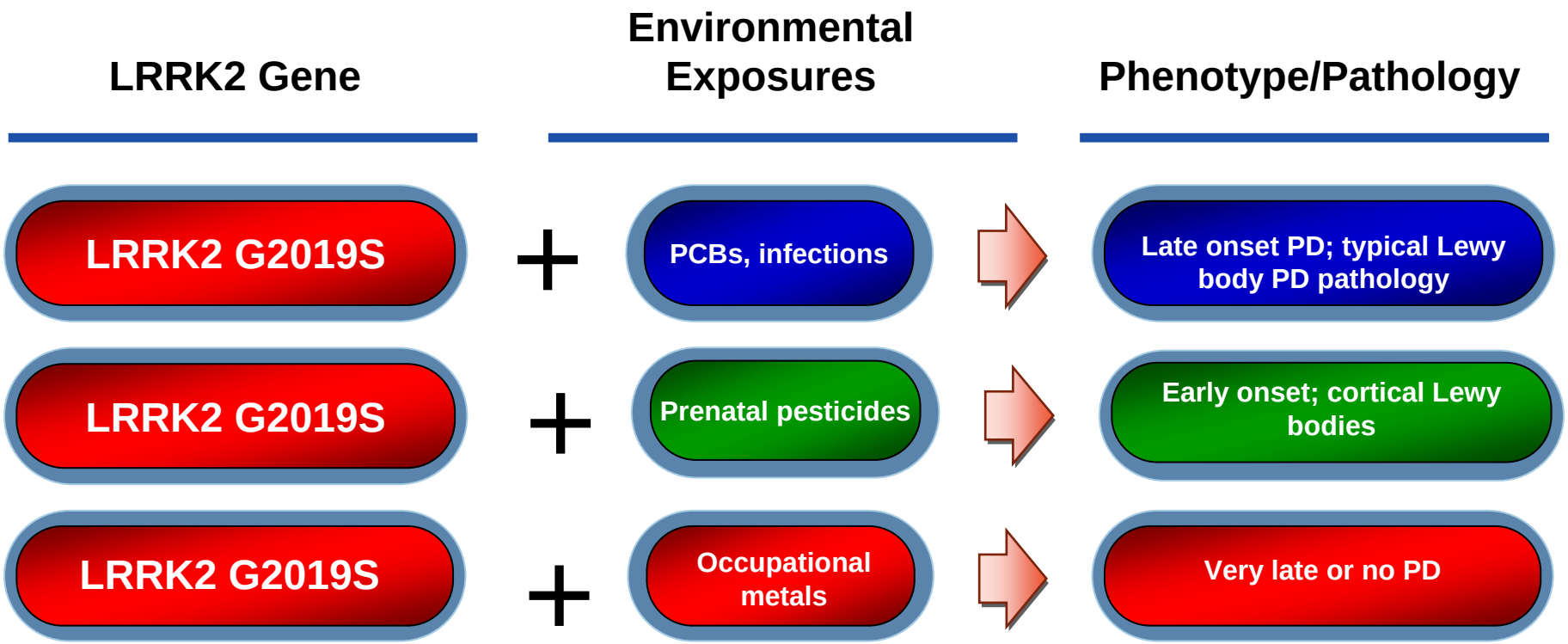
Emerging Genetic Findings in PD Create New Opportunities

LRRK2 and environmental exposures

- ***LRRK2*** **mutation causes a variable clinical and pathological phenotype**
- **The variable phenotype and the wide range in onset age suggest that other genetic variation, environmental exposures, and/or stochastic events modulate *LRRK2*-linked disease**

Zimprich. Neuron 2004; 44:601
Taylor. Science, 2006

Environmental Exposures Can Simplify Complex Diseases



Priorities for Program Development at NIEHS

- **Impact on Human Health and Disease**
  - **Focus on complex human diseases**
  - **Support interdisciplinary research**
- **Environmental Genomics**
  - **Genetic susceptibility**
  - **Comparative biology**
  - **Training in environmental genomics**
- **Environmental Biology Program**

Genes and Environment Initiative

- **Secretarial Initiative in FY2007 President's Budget**
- **2007-2010: $40 million/yr**
  - **$26 million human genetic case-control studies**
  - **$14 million environmental biology program**
- **Environmental Sciences Program – environment, diet, and activity level**
  - **Sensor technology**
  - **Biological response indicators**
  - **Workshop – Spring**

NIH coordinated
Centrally managed
Product oriented

	2006	2007	2008	2009	2010	TOTAL
Appropriation	----	14	14	14	14	56
NIEHS	4	8	10	10	----	32

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